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On May 5, 2003

TOWNSEND and TOWNSEND and CREW LLP

By: Paul Fauld Henley

PATENT
Attorney Docket No.: 2307AA-031220US
Client Ref. No.: 90-160-5

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Steinunn Baekkeskov *et al.*

Application No.: 08/838,486

Filed: April 7, 1997

For: IMPROVED METHODS FOR THE DIAGNOSIS AND TREATMENT OF DIABETES

Examiner: G. Ewoldt

Art Unit: 1644

DECLARATION OF STEINUNN BAEKKESKOV

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Steinnun Baekkeskov, state as follows:

(1) I am Professor of Medicine and Microbiology/Immunology, and Horan Markarian Chair of Diabetes at the University of California, an assignee of the above-captioned application. A copy of my curriculum vitae is attached as Exhibit A. I have actively conducted research in diabetes for over twenty years. I regularly read the scientific literature, particularly that relating to diabetes, attend scientific meetings, and am conversant with the view of many colleagues

(2) I have reviewed the above-captioned application of which I am a co-inventor and have followed the prosecution history thereof. I understand that the priority date of the application is September 7, 1990.

(3) The application is in large part premised on the discovery that glutamic acid decarboxylase (GAD) is a component of a pancreatic beta cell 64 kDa antigen that is a major autoantigen in insulin dependent diabetes mellitus (IDDM) (also known as type 1 diabetes). The application discloses administering GAD to a patient to treat or prevent IDDM. Administration of GAD induces tolerance to the 64 kDa autoantigen, thereby inhibiting or preventing further destruction of beta pancreatic cells, and the clinical symptoms of IDDM that eventually result from this destruction.

(4). When an antigen is administered to a subject, it can induce either a tolerogenic or an immune response depending on the regime with which it is administered. The application teaches that care should be taken not to potentiate an immune response. Based on my knowledge of the scientific literature, general principles for achieving a tolerogenic response rather than an immunogenic response were within the state of the art as of September 1990. For example, standard immunology textbooks available at he priority date of the invention discuss how either low or high dosages of antigen favor a tolerogenic response, whereas intermediate dosages favor an immunogenic response (Benjamini & Leskowitz, Immunology: A Short Course (Liss, 1988) at p. 256; Golub, The Cellular Basis of the Immune Response (2nd ed. Sinauer, 1981) at page 291). These textbooks also discuss how absence of adjuvant and use of unaggregated antigen favor a tolerogenic response It was also well known that intravenous administration generally favors induction of tolerance, (Cremer et al. Collagen induced arthritis in rats: antigen-specific suppression of arthritis and immunity by intravenously injected native type II collagen. J. Immunol. 131, 2995-3000 (1983); Scherer et al. Control of cellular and humoral immune responses by peptides containing T cell epitopes. Cold Spring Harbor Symp. Quant. Biol. 54, 497-504, 1989) This and other

routes of administration have been found successfully to induce tolerance in mice (see Harrison, *Molecular Medicine* 1, 722-727 (1994)). Given this guidance as to the different factors favoring immunogenic and tolerogenic response, and the teaching of the specification that a tolerogenic rather than an immunogenic response is required, I believe scientists in the IDDM field would be able to devise conditions to obtain a tolerogenic response without an immunogenic response as of September 1990.

(5) This expectation has been confirmed by numerous reports in the scientific literature in which administration of GAD has been shown to induce tolerance in NOD mice and prevent IDDM (see *e.g.*, Tisch *et al.*, *Nature* 366, 71-75 (1993)), Kaufman, *Nature* 366, 69-71 (1993), Tian *et al.*, *Nature Medicine* 12, 1348 (1996), Peterson *et al.*, *Diabetes* 44, 1478 (1994), and Pleau *et al.*, *J. Immunol. Immunopath.* 76, 90-95 (1995)). Several different parenteral routes of administration have successfully been used (see Harrison, *Molecular Medicine* 1, 722-727 (1994)).

(6) The NOD mouse is a good model of the major type of IDDM in which human patients develop autoantibodes and T cells to GAD, because NOD mice also develop autoantibodies and T cells to GAD (see Tisch *et al.*, *Nature* 366, 72-75 (1993) at *e.g.*, p. 21, column 1, first paragraph). The NOD mouse is a genetic strain of mouse that spontaneously develops autoimmunity to GAD, and subsequently symptoms of IDDM, in a manner similar to development of IDDM in humans. Positive results in the NOD mouse have been used as evidence to support human clinical trials of a number of drugs to treat IDDM. For example, human clinical trial of humanized OKT3 to treat IDDM is underway following a showing that such an antibody reversed hyperglycemia in NOD mice (see attached summary of the trial and Herold et al., New Engl. J. Med. 346, 1692-1698 (2002)). Similarly, a human clinical trial of alpha interferon is underway following a showing that alpha interferon was alpha interferon prevents diabetes in a NOD mouse (see attached summary of trial). Most importantly, the results using GAD to induce tolerance and prevent diabetes in the NOD mouse have been used as evidence to support

human clinical trials of a GAD vaccine to treat human type II diabetic patients (non-insulin dependent), who are treated with oral medication, but have autoantibodies to GAD, demonstrating that they are experiencing autoimmune destruction of ß cells and are therefore likely to become insulin dependent. The vaccine has been shown to be safe. The results of phase II of the clinical trials, which may provide an indication of the efficacy of the vaccine in preventing patients from becoming insulin dependent, will be announced at the American Diabetes Association annual meeting in New Orleans, June 13-17, 2003 (see attached summaries of trial).

(7) By contrast, the BB rat is not such a close model of IDDM in humans or other organisms that develop antibodies to GAD. The BB rat bears a genotype that results in spontaneous development of lymphocytopenia and clinical symptoms similar to those of IDDM. However, lymphocytopenia is not found in human IDDM. Furthermore, unlike the NOD mouse, and unlike most humans, the BB rat never develops autoimmunity to GAD (see Petersen *et al.*, Autoimmunity 25, 129-138 (1997) at p. 134, col. 1). Because the BB rat never develops autoantibodies to GAD, there is no reason to expect that therapeutic intervention with GAD would have any effect in the BB rat. Therefore, lack of such an effect in the BB rat, cannot be extrapolated to humans or other animals in which autoantibodies to GAD are present.

(8) In my opinion, the above evidence shows that a tolerogenic response has been obtained to GAD in mouse model of IDDM that is protective for IDDM and is predictive of similar response in humans. In my opinion, the evidence further shows this response was obtainable based on the teaching of the specification and common knowledge in the field as of September 1990.

(9) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false

(9) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

S. Baekkeskov

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Exhibit A

STEINUNN BAEKKESKOV

Curriculum Vitae

Affiliation	Professor of Medicine and Microbiology/Immunology Horan Markarian Chair of Diabetes
Address:	Hormone Research Institute/Diabetes Center, Box 0534 University of California, San Francisco San Francisco, CA 94143-0534

EDUCATION

1976:	Candidatus Scientarum, (M. Sc./Ph.D.degree) in Biochemistry from the University of Copenhagen, Denmark.
1984:	Licentiata scientarum, (Ph.D. degree) in Immunology from the University of Copenhagen, Denmark

PROFESSIONAL AND RESEARCH EXPERIENCE

1973-1975:	Thesis student, Department of Chemistry, The Carlsberg Laboratory, Copenhagen. Isolation characterization and chemical modification of enzymes from *Saccharomyces cerevisae*. Thesis: Characterization and chemical modification of glucose-6-phosphate dehydrogenase from Brewers yeast.
1976	Lecturer in Biochemistry, Department of Biochemistry, University of Copenhagen Medical School
1977-1979:	Postdoctoral Fellow, Department of Biochemistry, International Laboratory for Research on Animal Diseases (ILRAD), Nairobi, Kenya. Isolation and characterization of membrane proteins and lipids of African trypanosomes.
1980-1982:	Postdoctoral Fellow, Hagedorn Research Laboratory, Gentofte, Denmark. Research area: Immunology/cell and molecular biology of the pancreatic β-cell. The role of autoimmunity in the pathogenesis of insulin-dependent diabetes.
1982-1986:	Staff Scientist, Hagedorn Research Laboratory.
1986-1989:	Senior Staff Scientist, Hagedorn Research Laboratory (permanent position).
1987-1989:	Member of a panel of 6 Senior Staff Scientist that formed the Directory Board of the Hagedorn Research Laboratory.
1989-1992:	Assistant Professor, Department of Medicine, Department of Microbiology/Immunology, University of California, San Francisco
1992-1998	Associate Professor Department of Medicine, Department of Microbiology/Immunology, University of California San Francisco.
1998-present	Professor of Medicine and Microbiology/Immunology, University of California San Francisco
1990-1992:	Member of UCSF Graduate Program in Endocrinology
1992-date:	Member of UCSF Graduate Program in Molecular Medicine in PIBS
1992-date:	Member of UCSF Biomedical Sciences Graduate Program
1993-date:	Member of UCSF Graduate Program in Immunology in PIBS
1994-date:	Member of UCSF Graduate Program in Cell Biology in PIBS

AWARDS AND HONORS

1970-1973	P. Wulff's Foundation Scholarship
1973-1975:	Carlsberg Foundation Research Student Fellowship Award
1982-1984:	Juvenile Diabetes Foundation Fellowship Award
1984-1987:	Juvenile Diabetes Foundation Career Development Award.
1991-1993	NIH-Shannon Award
1997-current	Horan Markarian Chair of Diabetes

PUBLICATIONS

Original Articles in Reviewed Journals:

1. Rovis, L. and **Baekkeskov, S**. Subcellular fractionation of *Trypanosoma brucei*. Isolation and characterization of plasma membranes. Parasitology **80**, 507-524 (1980).

2. **Baekkeskov, S.**, Kanatsuna, T., Klareskog, L., Nielsen, D.A., Peterson, P.A., Rubenstein, A.H., Steiner, D.F., and Lernmark, A. Expression of major histocompatibility antigens on pancreatic islet cells. Proc. Natl. Acad. Sci. USA **78**, 6456-6460 (1981).

3. Steffes, M.W., Nielsen, 0., Dyrberg, T., **Baekkeskov, S.**, Scott, J., and Lernmark, A. Islet transplantation in mice differing in the I and S subregions of the H-2 complex. Transplantation **31**, 476-479 (1981).

4. **Baekkeskov, S.**, Nielsen, J.H., Marner, B., Bilde, T., Ludvigsson, J., and Lernmark, A. Autoantibodies in newly diagnosed diabetic children immunoprecipitate specific human pancreatic islet cell proteins. Nature **298**, 167-169 (1982).

5. Dyrberg, T., **Baekkeskov, S.**, and Lernmark, A. Specific pancreatic β-cell surface antigens recognized by a xenogenic antiserum. J. Cell Biol. **94**, 472-477 (1982).

6. Dyrberg, T., Nakhooda, A.F., **Baekkeskov, S.**, Lernmark, A., Poussier, P., and Marliss, E.B. Islet cell surface antibodies and lymphocyte antibodies in the spontaneously diabetic "BB" Wistar rat. Diabetes **31**, 278-181 (1982).

7. Kanatsuna, T., **Baekkeskov, S.**, Lernmark, A., and Ludvigsson, J. Immunoglobulin from insulin-dependent diabetic children inhibits glucose-induced insulin disease. Diabetes **32**, 520- 524 (1983).

8. **Baekkeskov, S.**, and Lernmark, A. Glucose stimulates the biosynthesis of a human pancreatic islet cell protein, detected by an antiserum against the human erythrocyte glucose transporter. FEBS Letters **157**, 331-335 (1983).

9. **Baekkeskov, S.**, Dyrberg, T., and Lernmark, A. Autoantibodies against an Mr 64K islet cell protein precede the onset of insulin-dependent diabetes in the BB-rat. Science **224**, 1348-1350 (1984).

10. **Baekkeskov, S**. and Lernmark, A. A β-cell glycoprotein of Mr 40,000 is the major rat islet cell immunogen following xenogenic immunization. Diabetologia **27**, 70-73 (1984).

11. Gerling, I., **Baekkeskov, S.**, and Lernmark, A. Islet cell and 64K autoantibodies are associated with plasma IgG in newly diagnosed insulin-dependent diabetic children. J. Immunol. **137**, 3782-3785 (1986).

12. **Baekkeskov, S.**, Landin, M., Kristensen, J.K., Srikanta, S., Bruining, G.J., Mandrup-Poulsen, T., de Beaufort, C., Soeldner, J.S., Eisenbarth, G., Lindgren, F., Sundquist, G., and Lernmark, A. Antibodies to a Mr 64,000 human islet cell antigen precede the clinical onset of insulin-dependent diabetes. J. Clin. Invest. **79**, 926-934 (1987).

13. Efrat, S., **Baekkeskov, S.**, Lane, D., and Hanahan, D. Coordinate expression of SV40 large T and p53 proteins in β-cells of transgenic mice harboring hybrid insulin-large T antigen genes. Embo J. **6**, 2699-2704 (1987).

14. Warnock, G.L., Ellis, D., Rajotte, R.V., Dawidson, I., **Baekkeskov, S.**, and Egebjerg J. Studies on the isolation and viability of human islets of Langerhans. Transplantation **45**, 957-963 (1988).

15. Christie. M., Landin-Olsson; M., Sundkvist, G., Dahlquist, G., Lernmark, A. & **Baekkeskov, S.** Antibodies to a Mr 64,000 islet cell protein in Swedish children with newly diagnosed type 1 (insulin dependent diabetes. Diabetologia **31**, 597-602 (1988).

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technique for isolating physiologically representative cell lines. Mol. Cell. Biol., **13**, 4223-4232. (1993).

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37. Hensch, T. K., Fagiolini, M., Mataga, N., Stryker, M. P., **Baekkeskov, S.**, and Kash, S. F. Local GABA circuit control of experience-dependent plasticity in developing visual cortex. Science **282**, 1504-1508 (1998).

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31. Tian, N., Petersen C., Kash, S. F., **Baekkeskov, S.**, Copenhagen, D. and Nicoll, R. The role of the synthetic enzyme GAD65 in the control of neuronal GABA release. Proc. Natl. Acad. Sci. USA, **96**, 12911-12916, (1999).

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36. Shi, Y., Kanaani, J., Menard-Rose, V., Ma, Y-H., Chang, P-Y, Hanahan, D., Grodsky, G., and **Baekkeskov, S.** Increased expression of glutamic acid decarboxylase and GABA in pancreatic β-cells impairs glucose-stimulated insulin secretion at a step proximal to membrane depolarization. Am. J. Physiol. Endocrinol. Metab. **279**, 684-694, (2000).

37. Wolfe, T., Bot, A., Hughes, A., Möhrle, U., Rodrigo, E., Jaume, J. C., **Baekkeskov, S.**, and von Herrath, M. Endogenous expression of autoantigens influence success or failure of DNA immunizations to prevent type 1 diabetes: addition of IL-4 increases safety. Eur. J. Immunol. **32**, 113-121. 2002.

38. Jaume, J. C., Parry, S. L., Madec, A.-M., Sønderstrup, G., and **Baekkeskov, S.** Suppressive effect of GAD65-specific autoimmune B lymphocytes on processing of T cell determinants located within the antibody epitope. J. Immunology **169**, 665-672, 2002.

39. Kanaani, J., El-Husseini, A. E-D., Aguilera-Moreno, A., Diacovo, J. M., Bredt, D. S., and **Baekkeskov, S.** A combination of three distinct trafficking signals mediates axonal targeting and presynaptic clustering of GAD65. J. Cell Biol. **158**, 1229-1238. 2002.

40. Hayakawa, N., Premawaedhana, L.D.K.E., Powell, M., Masuda, M.. Arnold, C., Sanders, J., Evans, M., Chen, S., Jaume, J. C., **Baekkeskov, S.**, Rees Smith, B. and Furmaniak, J. Isolation and characterization of human monoclonal autoantibodies to glutamic acid decarboxylase. Autoimmunity **35**, 343-355, 2002.

Symposia Papers, Reviews, and Book Chapters:

1. Lernmark, A. and **Baekkeskov, S.** Islet cell antibodies - theoretical and practical implications. Diabetologia **21**, 431-435 (1981).

2. Lernmark, A., Bonnevie-Nielsen, V., **Baekkeskov, S.**, Dyrberg, T., Kanatsuna, T., and Scott, J. Islet cell antibodies. **In:** Etiology and pathogenesis of insulin-dependent diabetes mellitus, eds.: J.M. Martin, R.M. Ehrlich, and F.J. Holland, Raven Press, N.Y., pp. 61-71 (1981).

3. **Baekkeskov, S.**, Dyrberg, T., Kanatsuna, T., Lernmark, A., Takei, I., and Soderstrum, K. The significance of ICSA in IDDM among Caucasians. **In:** Proceedings of the International Symposium on Clinico-Genetic Genesis of Diabetes Mellitus, Kobe, Feb. 11-12, 1982, eds.: G. Mimura, S. Baga, Y. Goto, and J. Kobberling, Excerpta Medica, Amsterdam, pp. 137-141 (1982).

4. **Baekkeskov, S.** and Lernmark, A. Rodent islet cell antigens recognized by antibodies in sera from diabetic patients. Acta Biol. Med. Germ. **41**, 1111-1115 (1982).

5. Brogren, C.H., **Baekkeskov, S.**, Dyrberg, T., Lernmark, A., Marner, B., Nerup, J., and Papadopoulos, G.K. Role of islet cell antibodies in the pathogenesis of type I diabetes. **In:** Diabetes and Immunology: Pathogenesis and Immunotherapy, eds.: H. Kolb, G. Schernthaner, and F.A. Gries, Hans Hubert Publishers. Berlin, pp. 65-78 (1983).

6. **Baekkeskov, S.** Radiolabelling and immunoprecipitation of islet cell antigens. **In:** Methods in Diabetes Research, Volume I, part A, eds.: J. Larner and S.L. Pohl, John Wiley & Sons, Ltd., New York, pp. 129-140 (1984).

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